EFSA's Opinions on risks to health posed by BPA: methodological considerations

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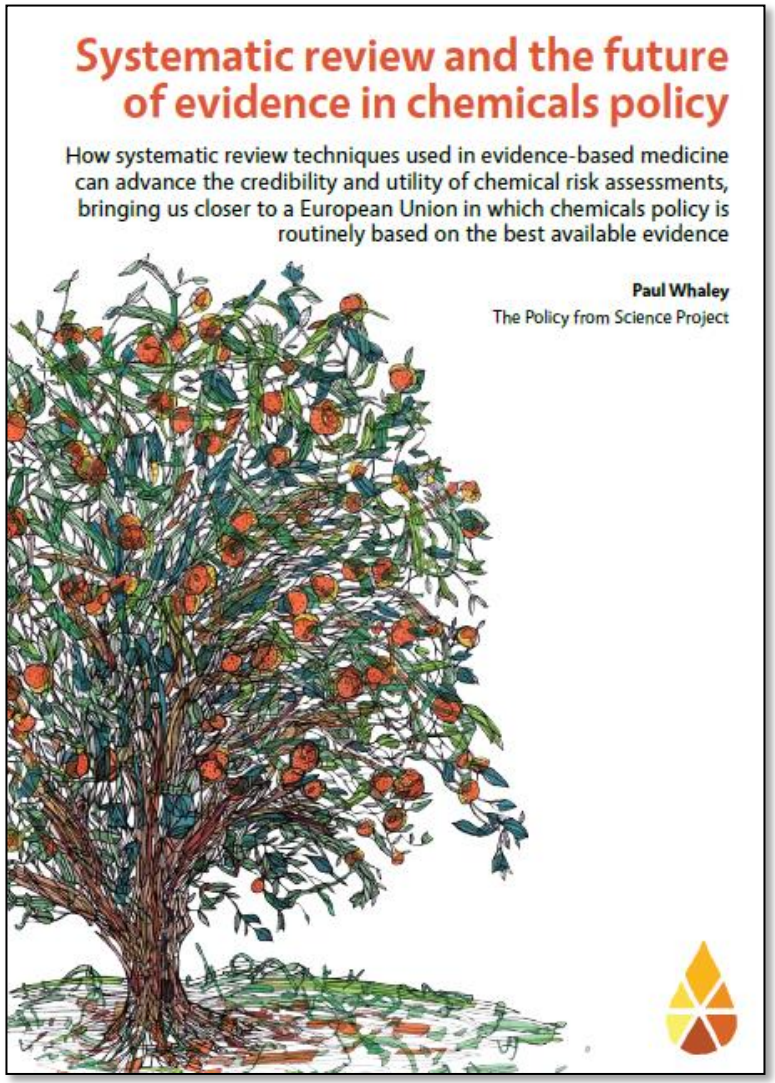
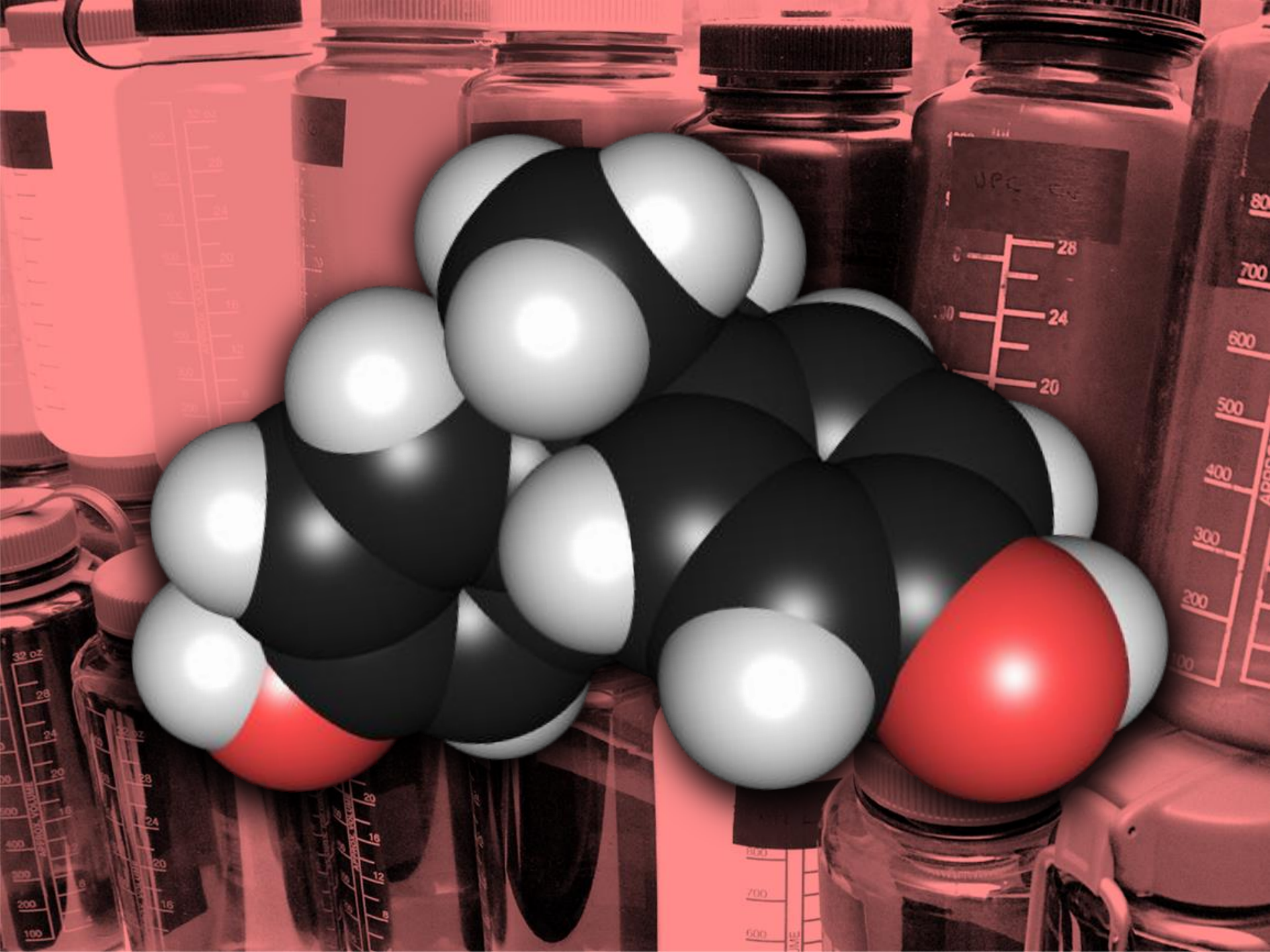
About me

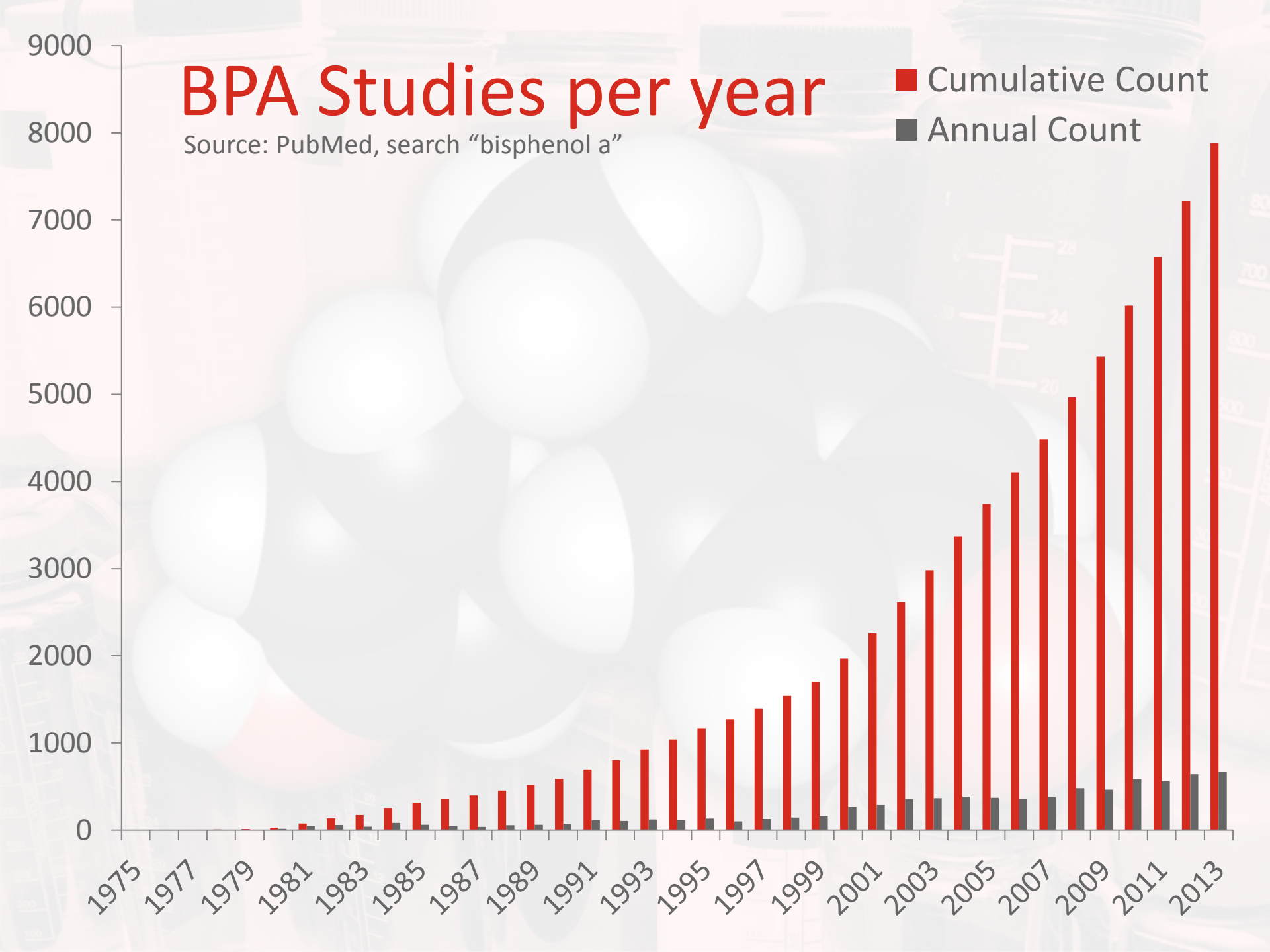
- Environmental consultant working mainly with NGOs
- Interested in methods for improving processes for reviewing evidence in chemical risk assessment
- Report about how systematic review methods used in medicine could contribute to advancing the accuracy of chemical risk assessments
- BPA is a great case study of one aspect of what is going wrong with analysis of science behind policy-making

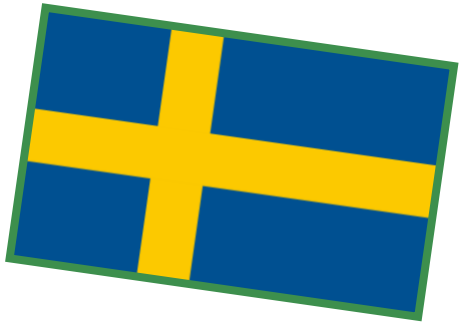




BPA Studies per year

Source: PubMed, search “bisphenol a”





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efsa
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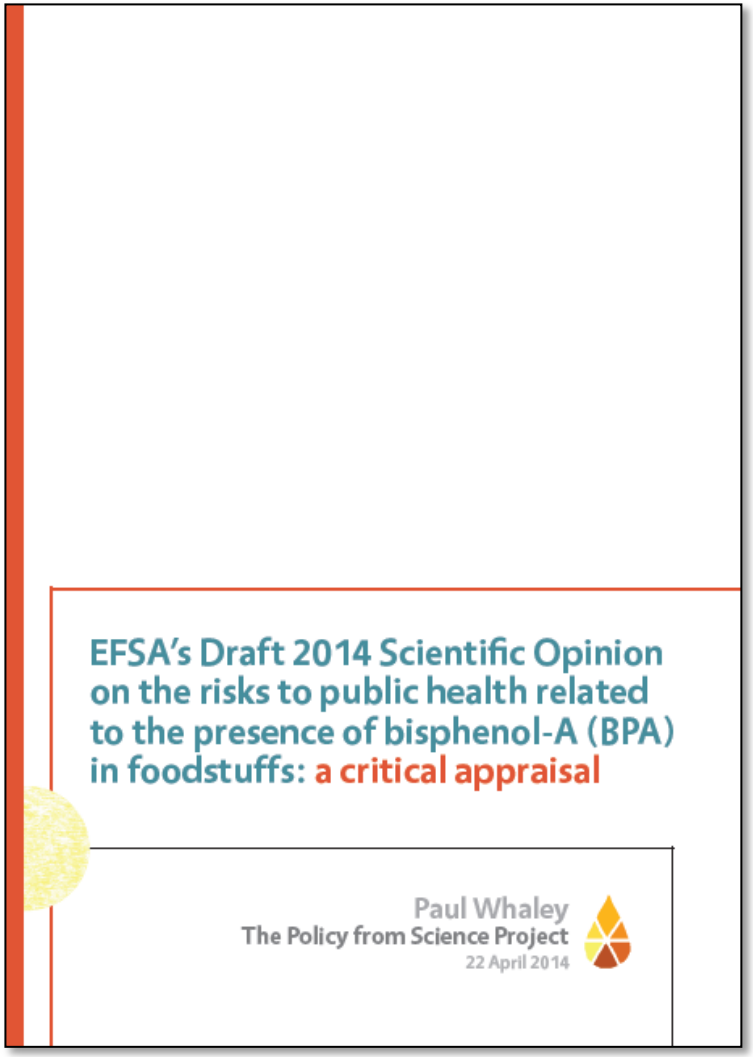
Today's talk

- My analysis of EFSA's 2014 Draft Opinion on risks to health posed by bisphenol-A (BPA)



Overview

- **Objective**: Evaluate the methodological quality of EFSA's reviews of risks to health posed by BPA
- **Method**: Develop a novel toolkit for appraising the methodological quality of literature reviews, derived from best practice in evidence-based medicine
- **Results**: EFSA risk assessments of BPA are either not conducted according to a scientifically robust methodology, or are insufficiently documented as to be able to determine one way or the other
- **Recommendation**: Develop systematic review tools for valid, reproducible synthesis of toxicological research in risk assessment


We are, through the media, as ordinary citizens, confronted daily with controversy and debate across a whole spectrum of public policy issues. But typically, we have no access to any form of systematic ‘evidence base’ — and therefore no means of participating in the debate in a mature and informed manner.
Prof. Sir Adrian Smith

Bisphenol-A: Who to believe?

How do you evaluate a review?

- What distinguishes a good review from a poor one?

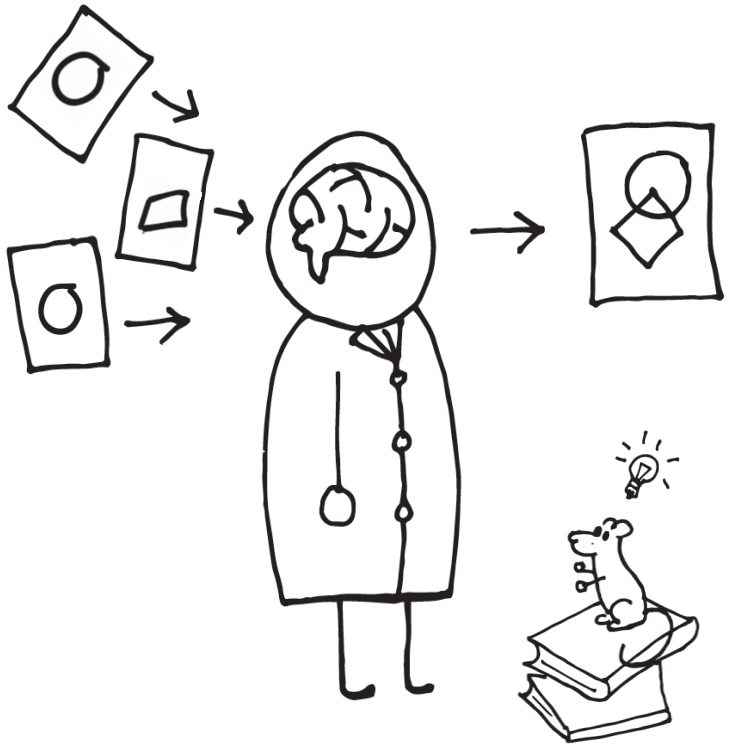
Several toolkits in medicine

Shortcomings of existing tools

- Incomplete in terms of targets of assessment
- Unclear rationale for targets of evaluation (e.g. use of at least two reviewers)
- Conflation of reporting with performance (something being done vs. it being done well)
- Lack of high-quality guidance notes or elicitation mechanisms to help users with appraisal
- Not intended for reviews in toxicology

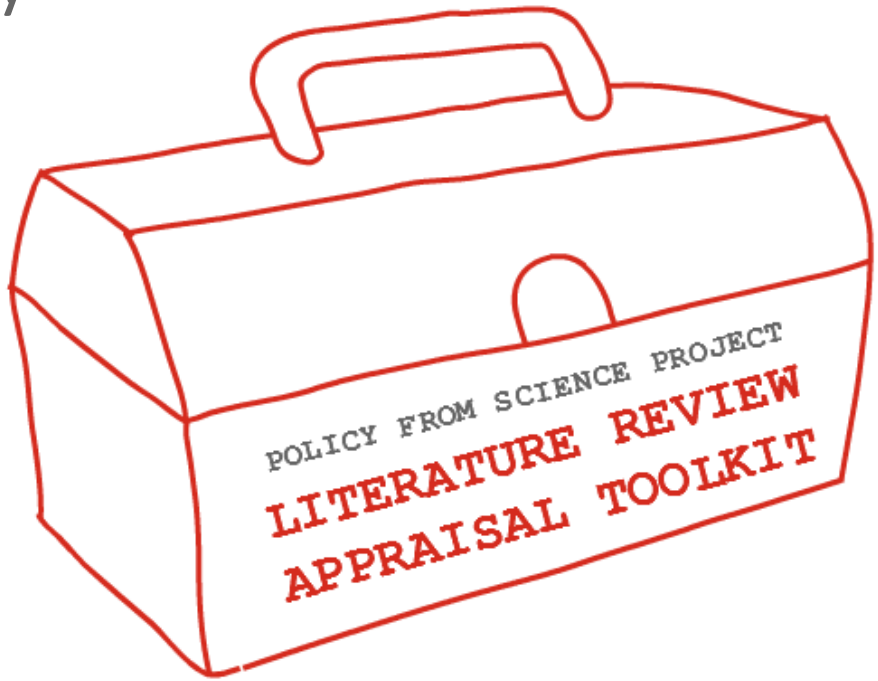
New toolkit needed

- Developed from appraisal tools and best practice guidelines for conducting reviews in medicine
- e.g. CASP, PRISMA, NICE, AMSTAR and Cochrane Collaboration guidance on review methods (n=11)

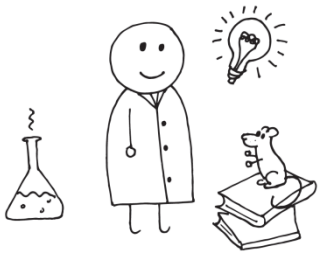


So anyway, one year later …

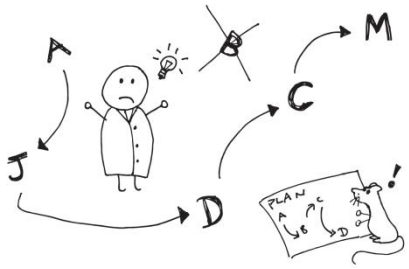
- **Literature Review Appraisal Toolkit (LRAT)**
- 9 evaluable domains relevant to the methodological quality of toxicological literature reviews



1. Clear objective

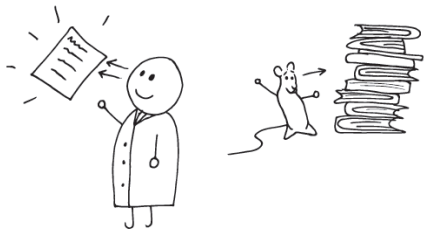


2. Prepub'd protocol



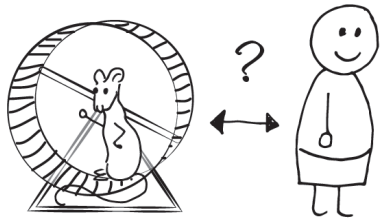
3. Interests & contribs

4. Search strategy



5. Selection criteria

6. External validity*

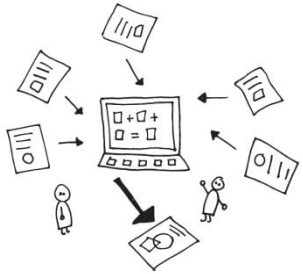


*test of relevance

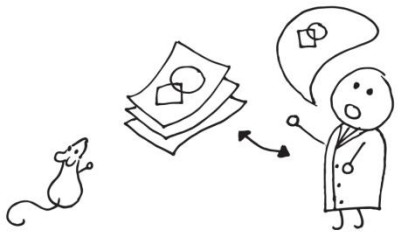
7. Internal validity*

*test of reliability

8. Synthesis of data



9. Accurate summation



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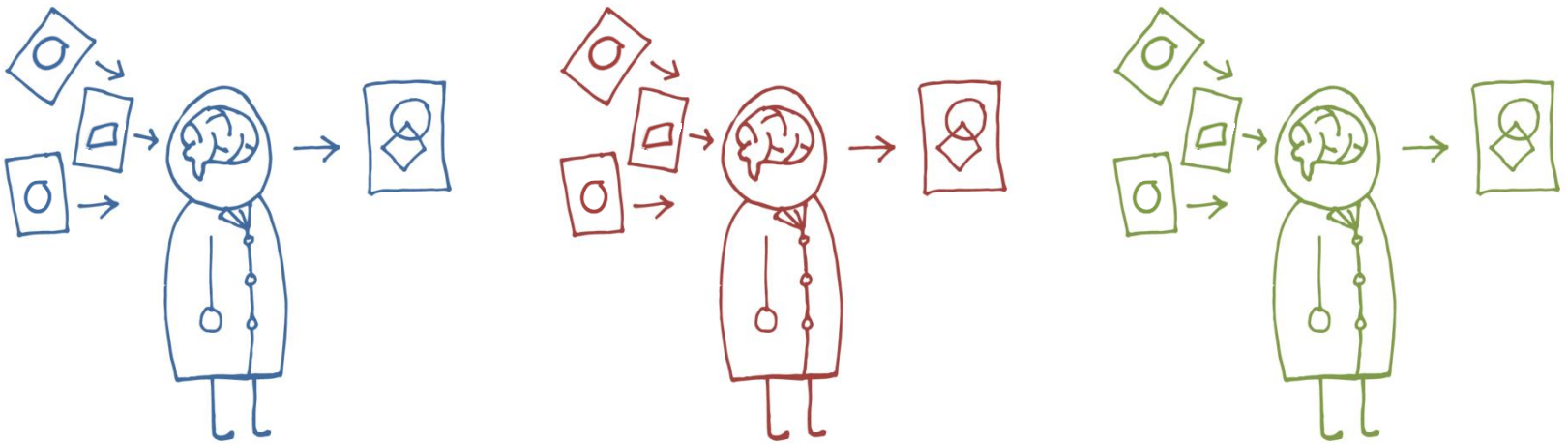
/LRAT

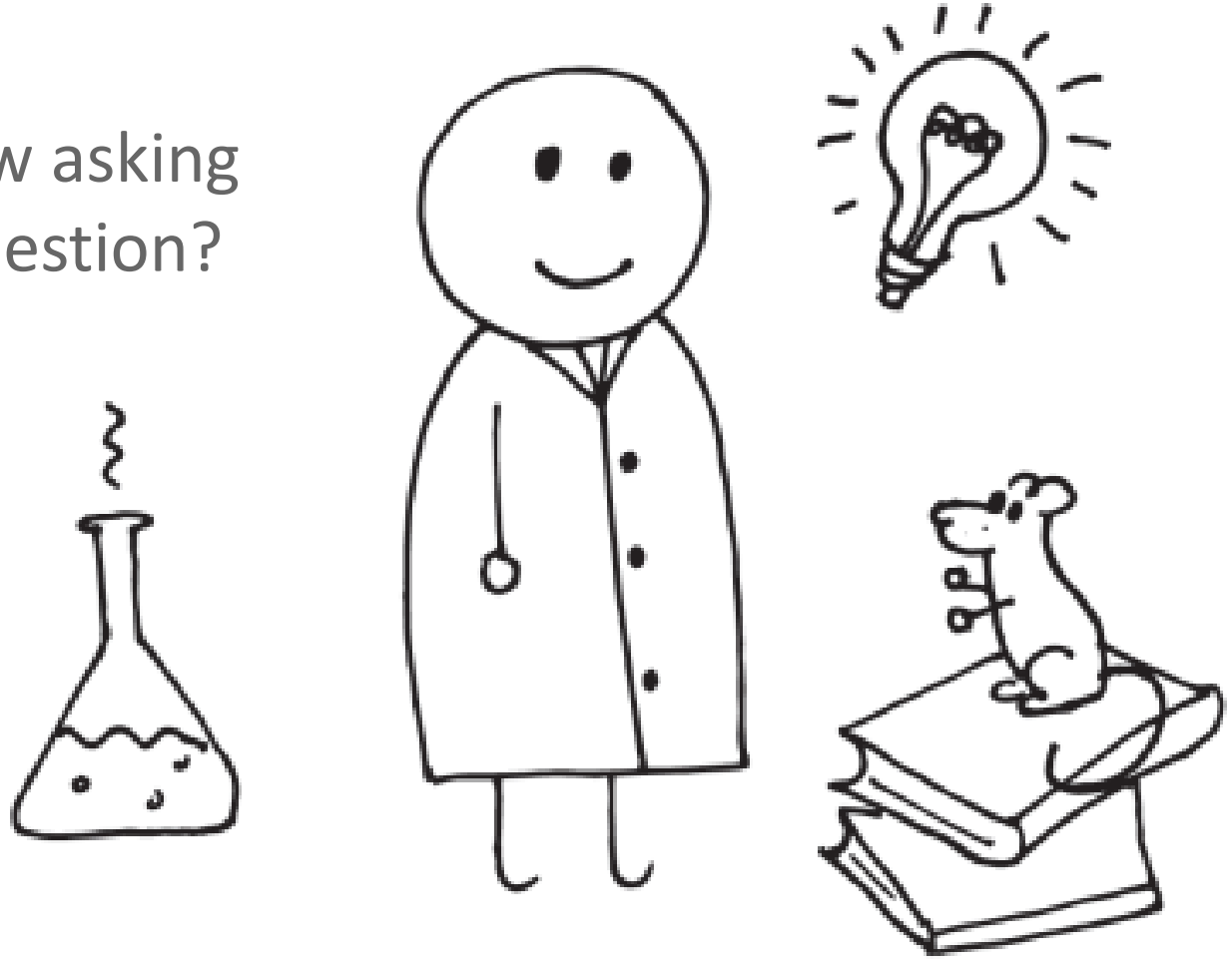
Target of evaluation

- Utility (is the review useful?)
- Reproducibility (are the methods transparent?)
- Validity (are the results correct?)



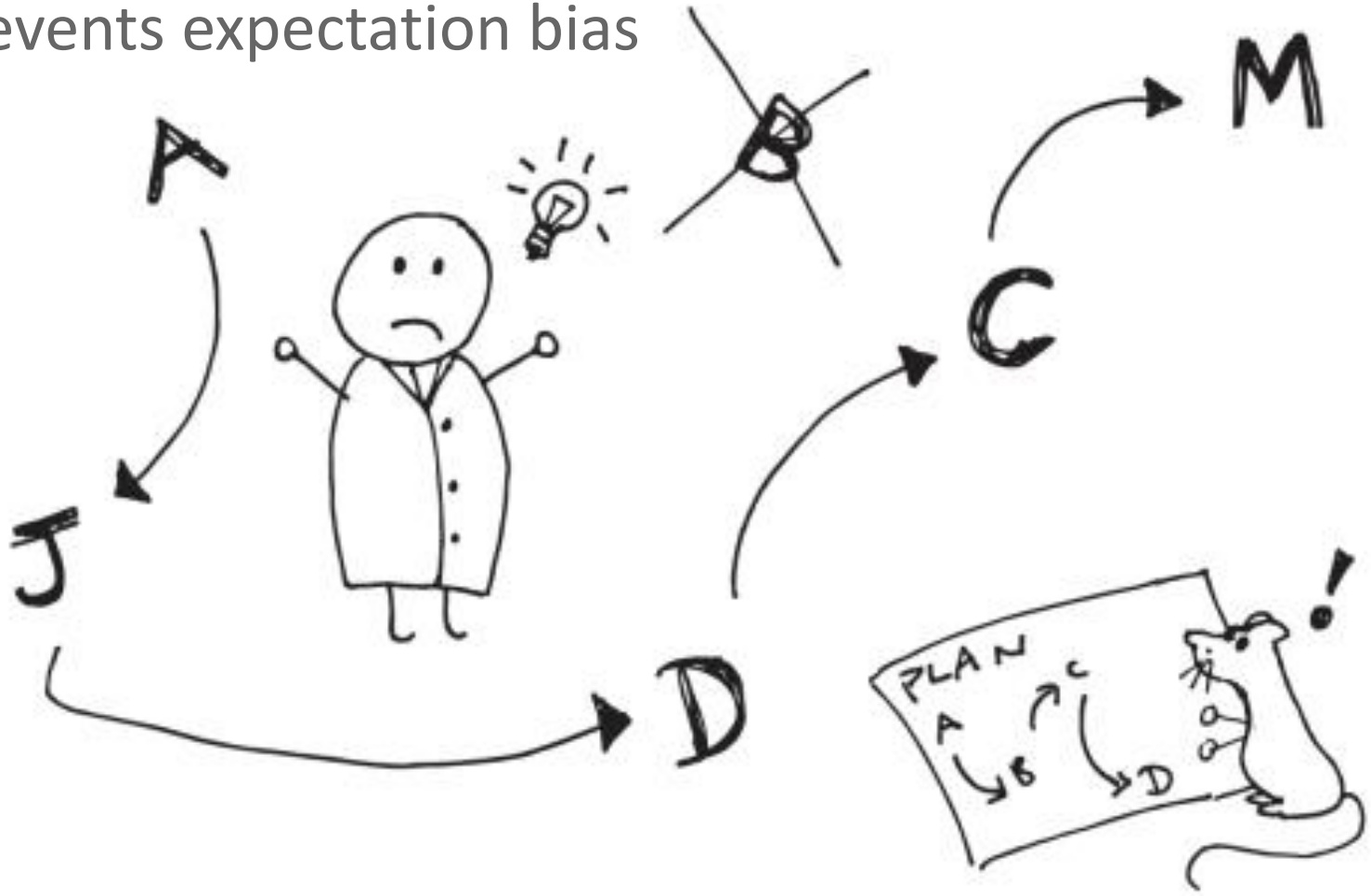
1. Clear Objective

Is the review asking the right question?



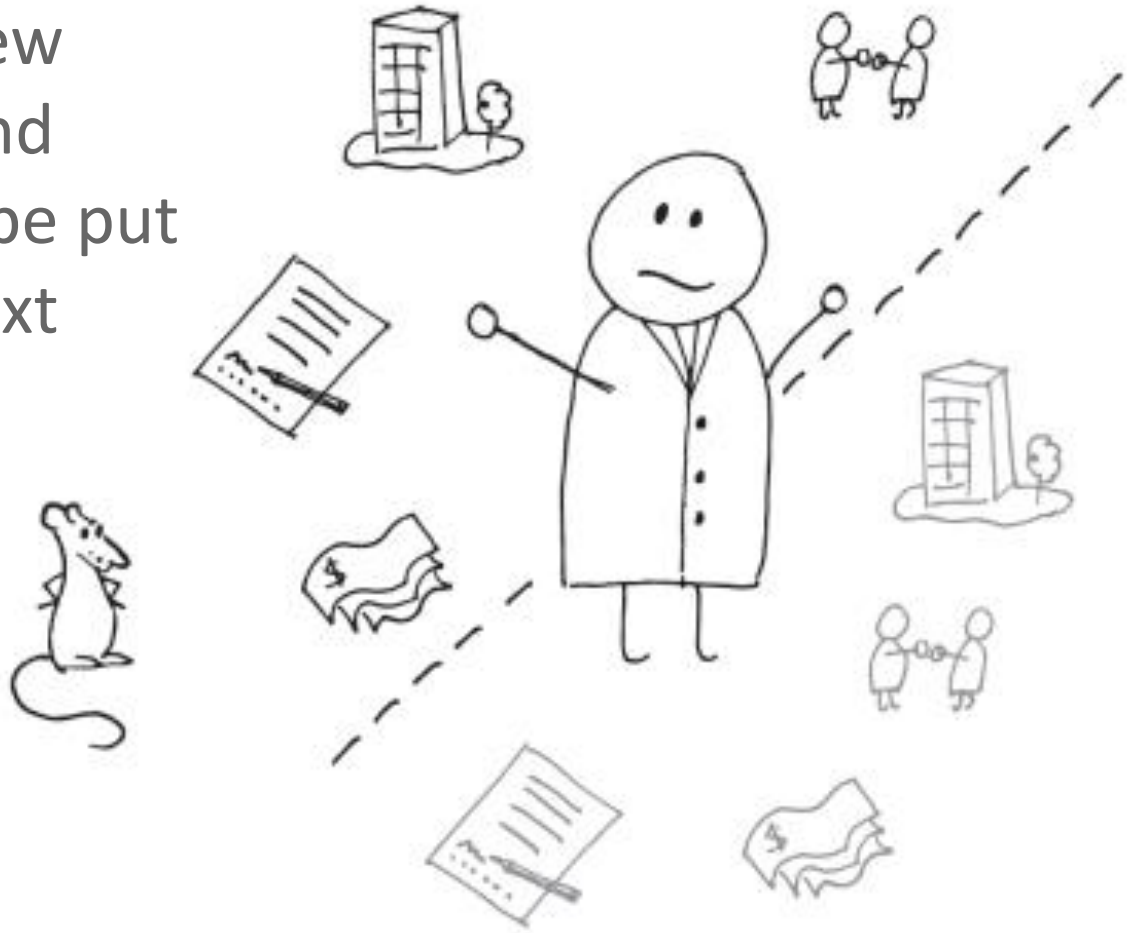
2. Pre-published protocol

Prevents expectation bias



3. Declaration of interests

Allows review objective and findings to be put in full context



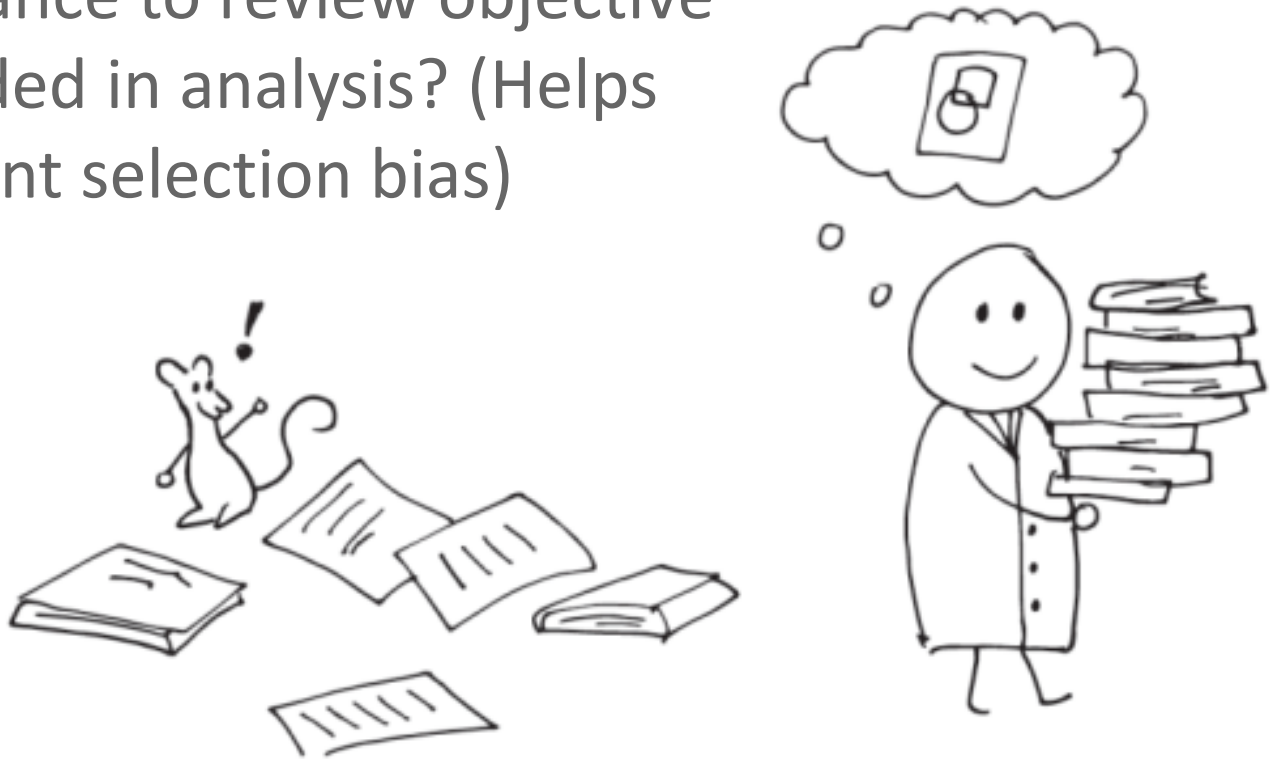
4. Search strategy

Have all studies of possible relevance to review objective have been found?

(Helps preventing sampling bias)

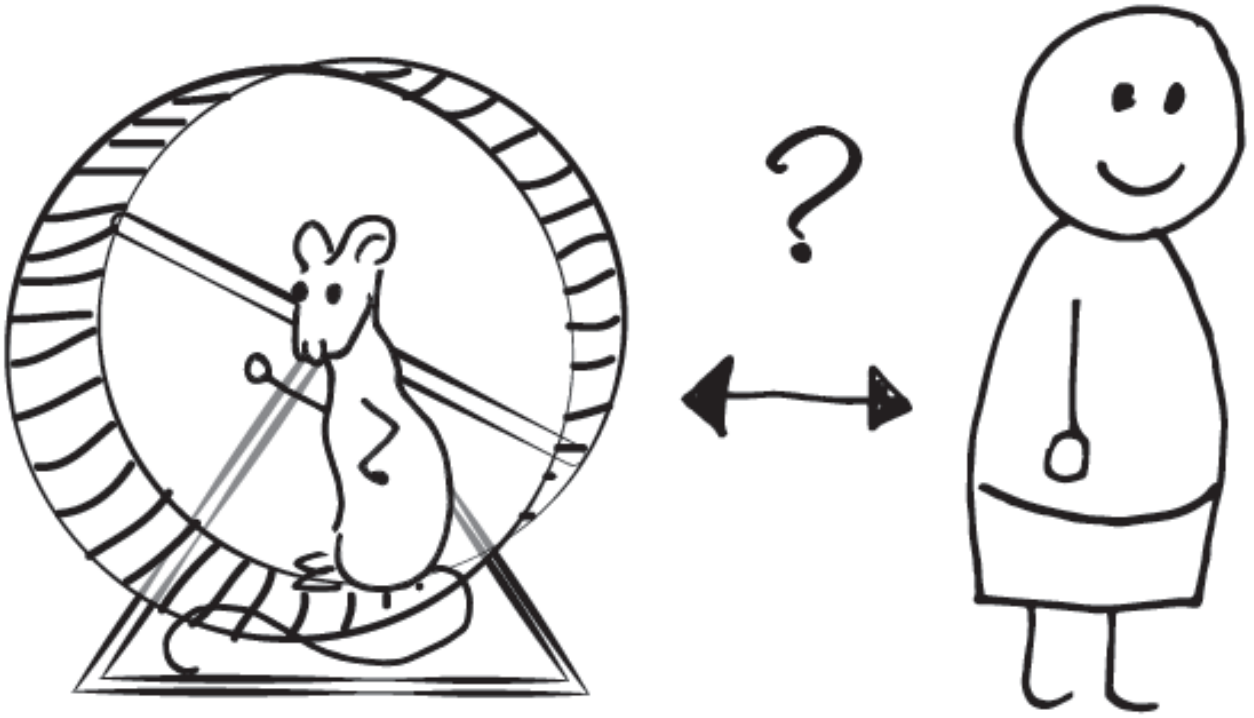
5. Selection criteria

Have all studies of actual relevance to review objective included in analysis? (Helps prevent selection bias)



6. Fair test of *external validity**

*relevance



To consistently put more weight on the studies of greater direct relevance to the review objective

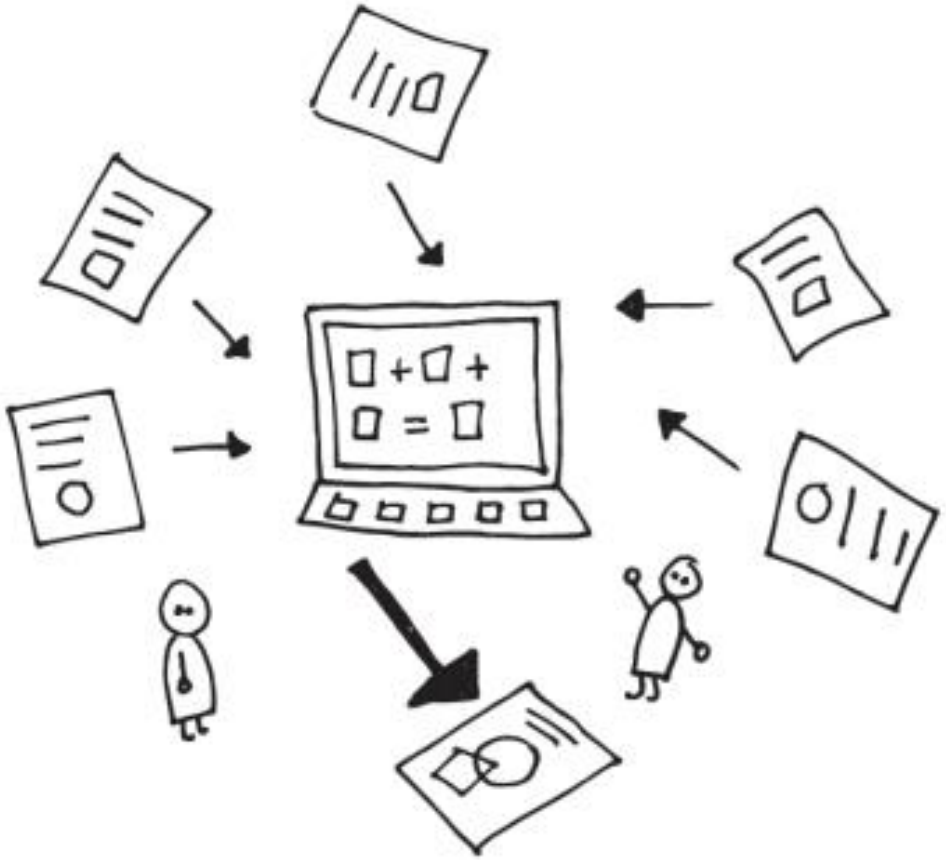
7. Fair test of *internal validity**

*reliability

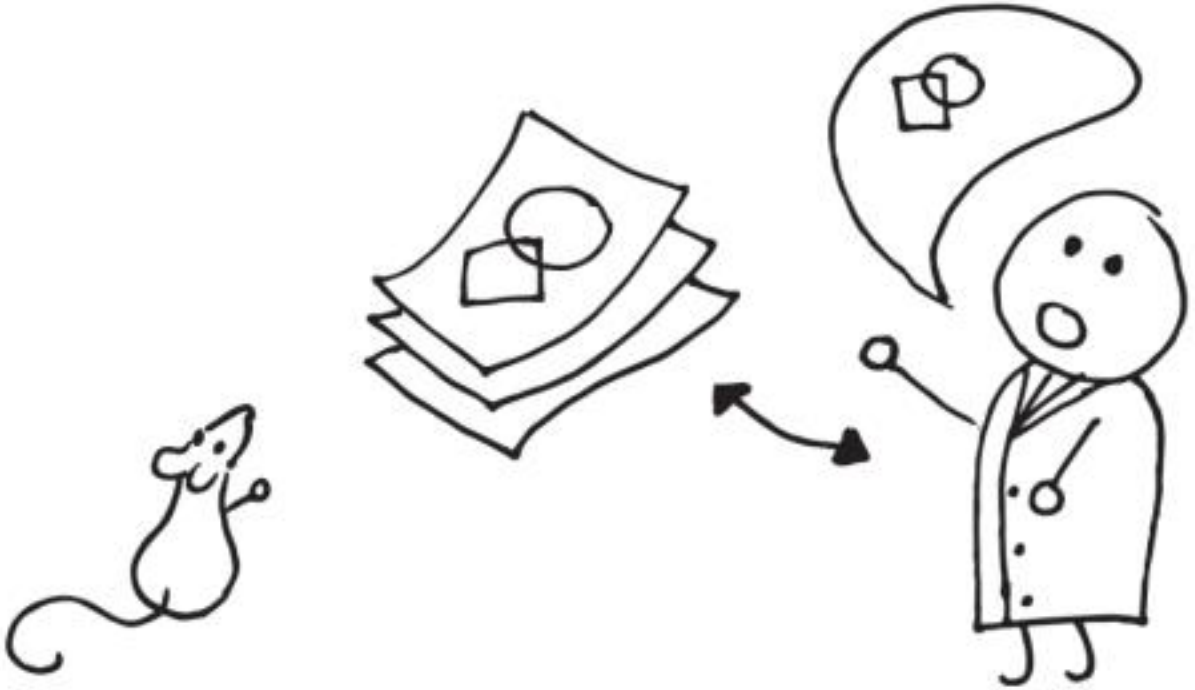
To consistently put more weight on the better studies and less on the worse

8. Synthesis of evidence

Distillation of results into a valid statement of what is and is not known in relation to the review objective



9. Summation of findings



The summary sections of a review should reflect what is expressed in the body of the review

Appraisal options

Satisfactory

Clear, valid and consistent procedure

Unclear

Insufficient documentation to evaluate

Unsatisfactory

Positive evidence of inconsistent
or invalid procedure

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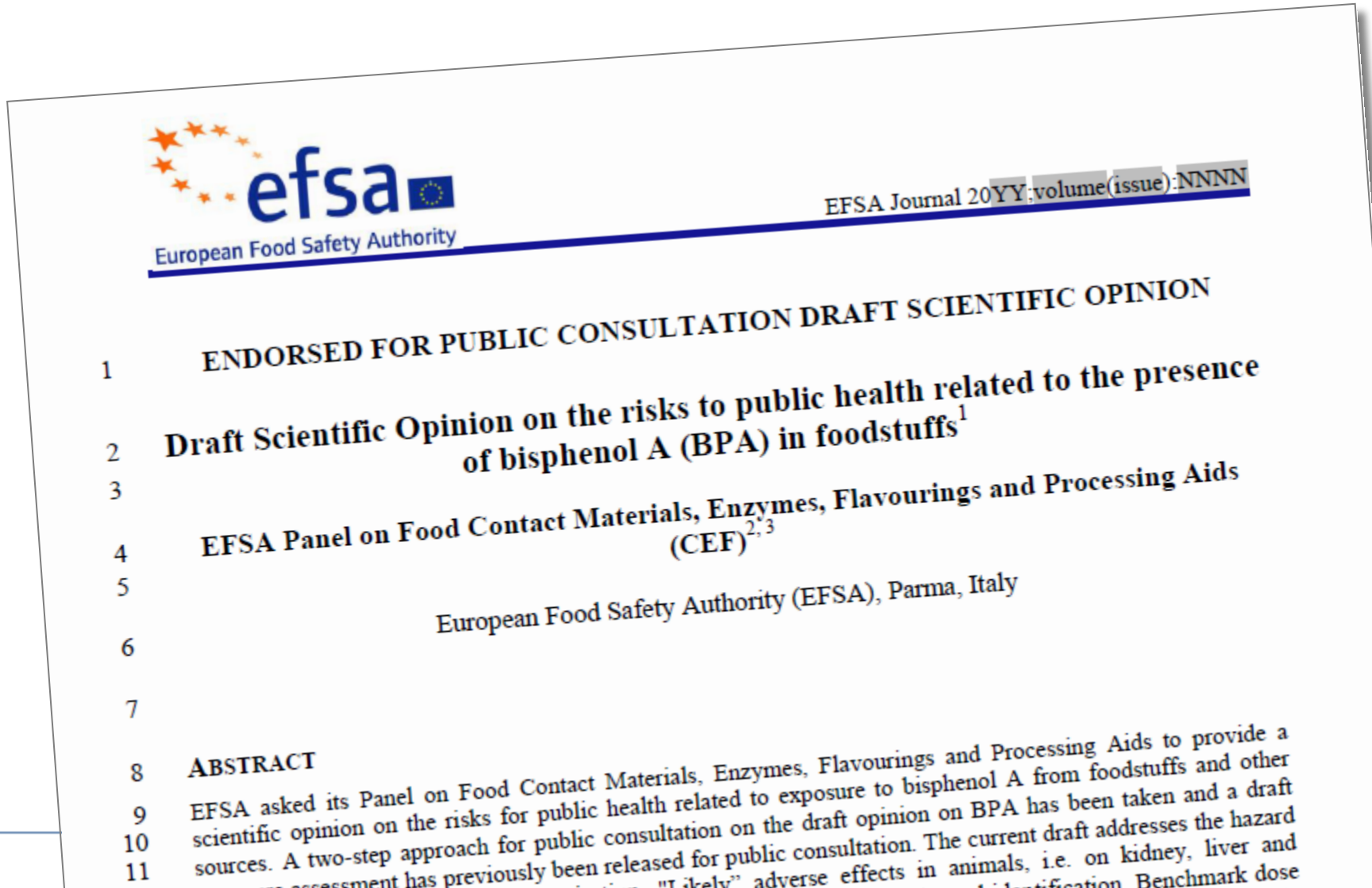
/LRAT

EFSA 2014 Draft Opinion on BPA



European Food Safety Authority

EFSA Journal 20YY;volume(issue):NNNN

ENDORSED FOR PUBLIC CONSULTATION DRAFT SCIENTIFIC OPINION

Draft Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs[1]

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

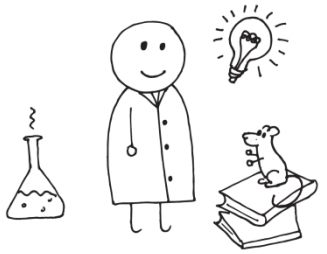
ABSTRACT

EFSA asked its Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids to provide a scientific opinion on the risks for public health related to exposure to bisphenol A from foodstuffs and other sources. A two-step approach for public consultation on the draft opinion on BPA has been taken and a draft assessment has previously been released for public consultation. The current draft addresses the hazard "Likely" adverse effects in animals, i.e. on kidney, liver and identification. Benchmark dose

Parma, we have a problem

	EFSA 2014 Draft Opinion on BPA
1. Objective	🟡
2. Protocol	🔴
3. Interests	🟡
4. Search Method	🔴
5. Study Selection	🔴
6. Relevance Test	🟡
7. Reliability Test	🔴
8. Synthesis	🟡
9. Answer	🟢

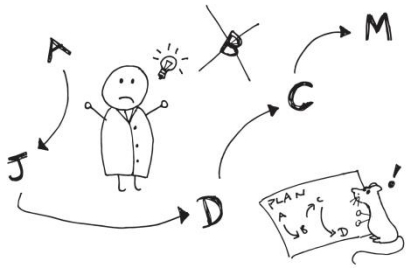
1. Objective



Unclear

- The stated objective of the Opinion is to collate the published evidence of hazards to health posed by BPA and interpret this into a dose-based risk assessment
- However, the hazard characterization section redirects the Opinion towards determining whether or not any individual study exists which warrants changing the tolerable daily intake (TDI) for BPA.

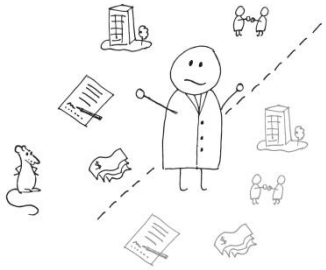
2. Pre-published protocol



Unsatisfactory

- There is no pre-published protocol

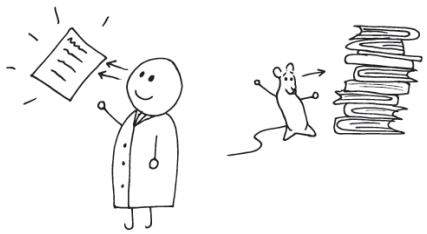
3. Declaration of interests



Unclear

- Difficult to obtain
- Have to be extrapolated from lengthy DOIs
- No declaration of contributions

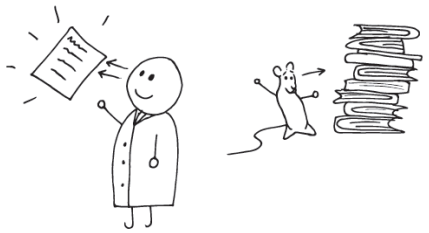
4. Search strategy



Unsatisfactory

- Literature search yields papers from 2010-2012 which are not referenced in the Opinion
- EFSA openly acknowledges partial search process for 2013 papers
- Unlike 2010, no list of search results!

Missing studies



- **Effects of prenatal and postnatal exposure to a low dose of bisphenol A on behaviour and memory in rats**. Gonçalves, Carjone Rosa; Cunha, Raquel Wigg; Barros, Daniela Marti; Martínez, Pablo Elías. Environmental Toxicology and Pharmacology, 2010
- **Anxiety- and Depressive-Like Behaviours in CD-1 Mice Developmentally Exposed to Bisphenol A**. Nelms, J; Ward, M; Meyer, A; Miller, M; Sable, H. Neurotoxicology And Teratology, 2011
- **The Effects of Maternal Exposure to Bisphenol A on Allergic Lung Inflammation into Adulthood**. Bauer, Stephen M; Roy, Anirban; Emo, Jason; Chapman, Timothy J; Georas, Steve N; Lawrence, B. Paige. Toxicological Sciences, 2012
- **Developmental exposure to bisphenol A leads to cardiometabolic dysfunction in adult mouse offspring**. Cagampang, F. R; Torrens, C; Anthony, F. W; Hanson, M. A. Journal of Developmental Origins of Health and Disease, 2012
- **The impact of neonatal bisphenol-A exposure on sexually dimorphic hypothalamic nuclei in the female rat**. Adewale, HB; Todd, KL; Mickens, JA; Patisaul, HB. Neurotoxicology, 2011
- **Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol A**. Poimenova A, Markaki E, Rahiotis C, Kitraki E. Neuroscience. 2010

5. Selection criteria

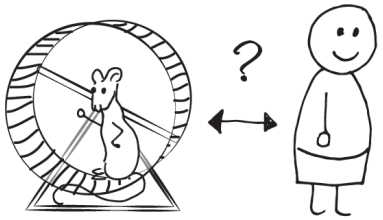
Unsatisfactory

- EFSA used a different selection process for including studies from 2013 (expert judgment of relevance to the review) than it did for studies from 2010-2012 (a specified list of inclusion criteria)

5.1 Furthermore …

- EFSA changed its mind about the inclusion criteria for the 2014 Opinion
- At the point of hazard characterisation, it excluded the mammary epithelial cell proliferation studies for having “methodological shortcomings” which make them unsuitable for calculating a TDI
- Even though they were good enough to show a likely hazard!

6. External validity



Unclear

- No explicit methodology, though directness of evidence is sometimes described in the appraisal of research
- Not clear what the criteria for relevance are, nor how they affect the weight given to a study in the overall analysis, nor if they are consistently applied

7. Internal validity

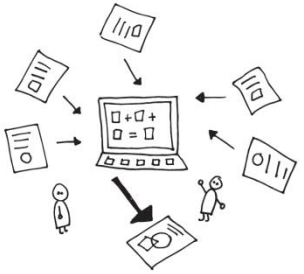
Unsatisfactory

- Criteria for methodological quality are not valid
- Insufficient evidence that the criteria are consistently applied
- It is not clear how fulfilment of the criteria translates into a judgment of reliability

Comments on internal validity

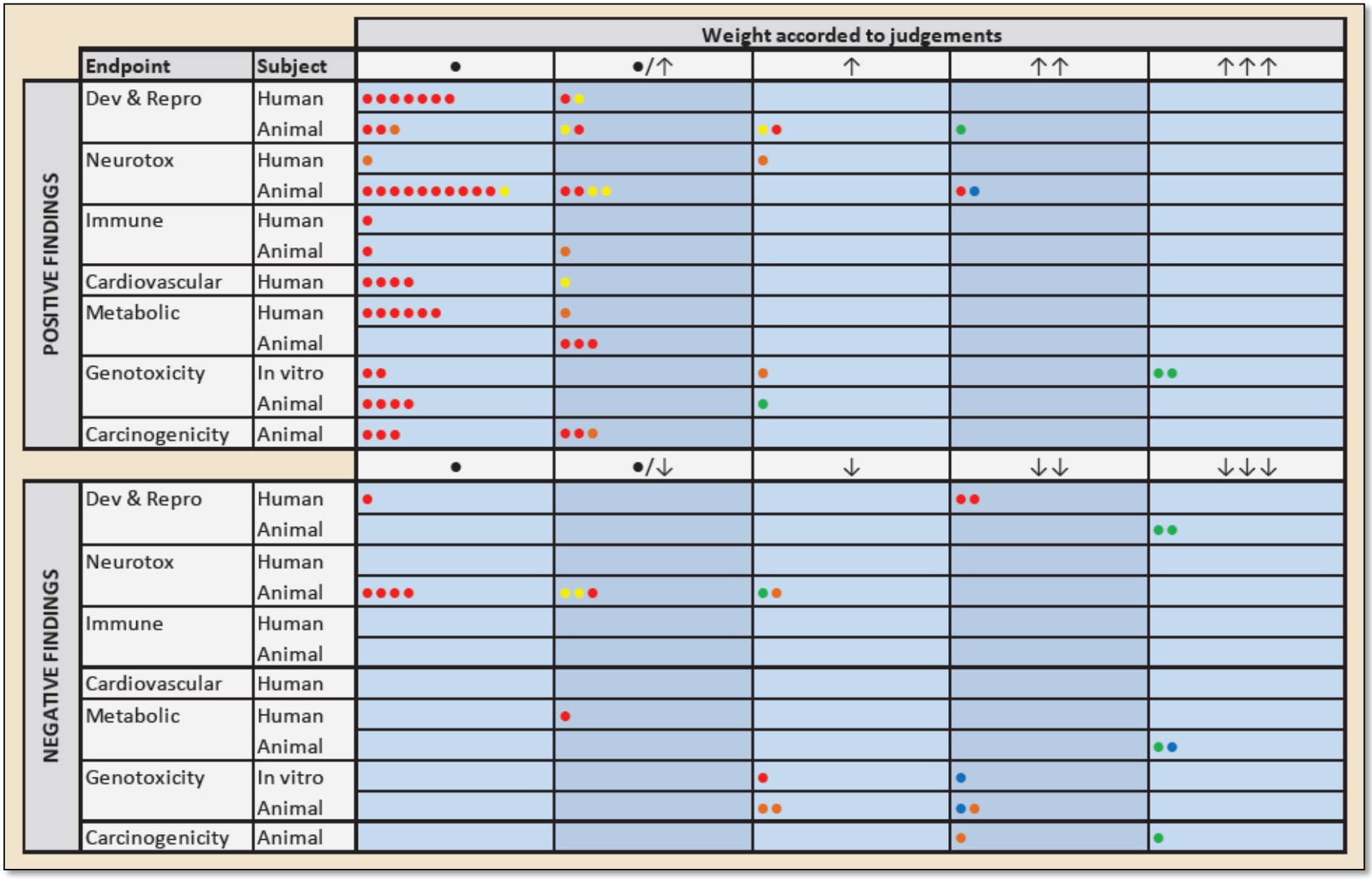
- Conflates of quantity of information with quality of research (single dose studies downgraded)
- Consistency of findings between studies is taken as an indicator of methodological quality
- Conflates reporting quality with methodological quality
- Conflates conformity with guidelines with methodological quality
- Doesn’t consider important aspects of methodological quality (e.g. random allocation)

8. Synthesis of evidence



Unclear

- Insufficiently documented
- Carefully documented but not at all clear how appraisal of studies is connected to attribution of weight in the WoE analysis


Weight accorded to judgements
Endpoint
Subject
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POSITIVE FINDINGS
Dev & Repro
Human
Animal
Neurotox
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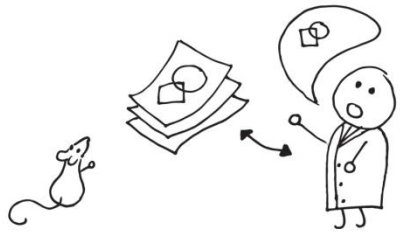
Animal

9. Summation of findings



Satisfactory

- Woopee!

Conclusions

- Search and selection methods are partial and risk biasing the results of the review
- The appraisal of methodological quality of included studies cannot distinguish better research from worse
- Weight-of-evidence analysis cannot be evaluated for validity
- EFSA has not actually conducted a coherent review of BPA toxicity, but instead only repeated its traditional TDI calculation, introduced by a lengthy but irrelevant hazard assessment

Analysis of EFSA Opinions on BPA

	2010 Opinion	2013 Draft Exp. Assessment	2014 Draft Opinion
1. Objective			
2. Protocol			
3. Interests			
4. Search Method			
5. Study Selection			
6. Relevance Test			
7. Reliability Test			
8. Synthesis			
9. Summation			

Science is supposed to be cumulative, but scientists only rarely cumulate evidence scientifically.

Chalmers, Hedges & Cooper (2002)

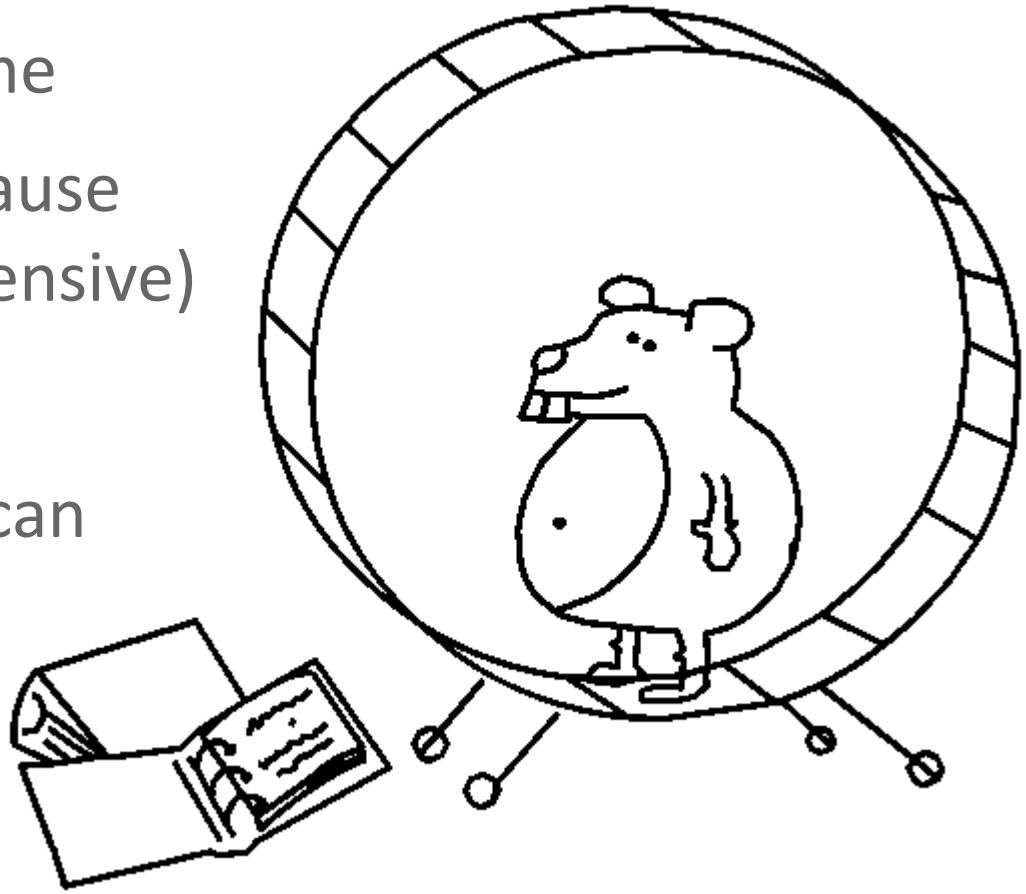

We are, through the media, as ordinary citizens, confronted daily with controversy and debate across a whole spectrum of public policy issues. But typically, we have no access to any form of systematic ‘evidence base’ — and therefore no means of participating in the debate in a mature and informed manner.
Prof. Sir Adrian Smith

How to improve literature reviews

- Apply systematic review methods used in evidence-based medicine to chemical risk assessment

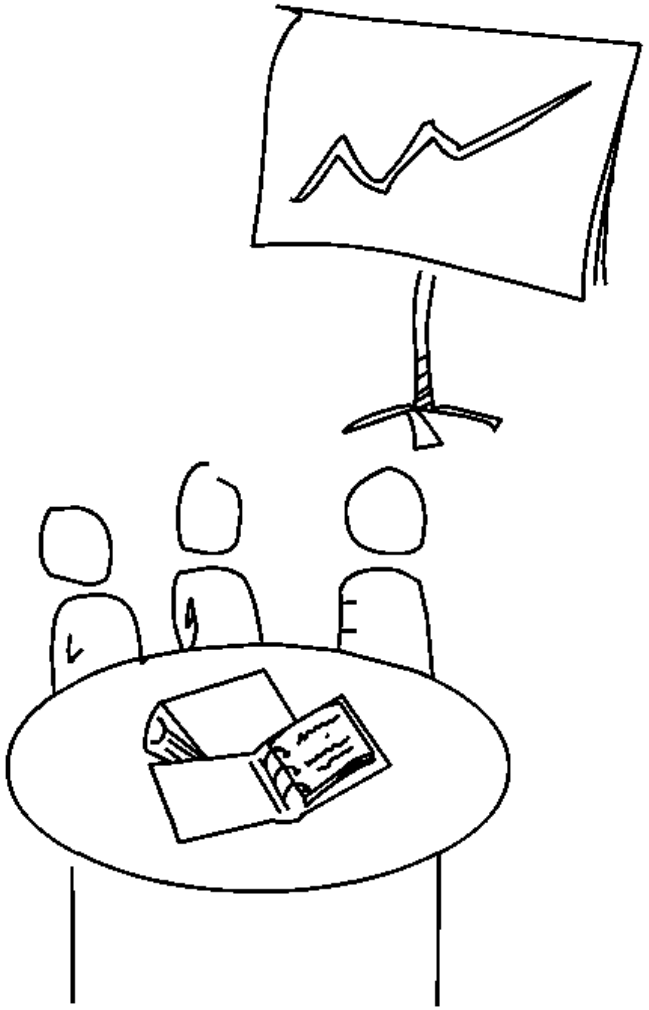
Research ❤ systematic review

- Manage data volume
- Cost-effective (because being wrong is expensive)
- ID knowledge gaps
- Know how far you can generalise
- Enhance credibility



Society ♥ systematic review

- Reduce harm to health & environment (accurate identification of risks)
- Reduce unnecessary economic costs (fewer false positives)
- Enhance credibility of institutions (produce readable, credible documents)



Democracy ❤ systematic review

- Access to systematic evidence-base rather then simply having to take on trust the pronouncements of experts
- Allows informed critique of policy options
- Participation in evidence-based decisions

Thank you

- Very
- Much
- Indeed
- Read my report
- Look at my website
- Research funding please, this is important